P1 1200577

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

August 04, 2004

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: ***60/470,420***
FILING DATE: ***May 15, 2003***
RELATED PCT APPLICATION NUMBER: *PCT/US04/12663*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

T. LAWRENCE
Certifying Officer

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(b)(2).

INVENTOR(s)/APPLICANT(s)

Given Name (first and middle [if any])	Family Name or Surname	Residence (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Cynthia W.	TUTHILL	645 Woodland Avenue, Menlo Park, CA 94025
Alfred R.	RUDOLPH	14142 Liddicoat Drive, Los Altos, CA 94022

☐ Additional inventors are being named on the ___ separately numbered sheets attached hereto.

TITLE OF THE INVENTION (280 characters max)

TREATMENT OR PREVENTION OF RESPIRATORY VIRAL INFECTIONS WITH ALPHA THYMOSIN PEPTIDES

CORRESPONDENCE ADDRESS

☒ Customer Number: **6449**

☐ Firm or Individual Name	Rothwell, Figg, Ernst & Manbeck, P.C.				
Address	1425 K Street, N.W.				
Address	Suite 800				
City	Washington	State	D.C.	ZIP	20005
Country	U.S.A.	Telephone	202-783-6040	Fax	202-783-6031

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* [7]
☐ Drawing(s) *Number of Sheets* [ ]
☐ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number ______
☐ Other *(specify)* ______

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☒ Applicant claims small entity status. See 37 CFR 1.27
☐ A check or money order is enclosed to cover the filing fee
☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 02-2135
☐ Payment by credit card. Form PTO-2038 is attached.

Filing Fee Amount: **$80.00**

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: ______

Respectfully submitted,

SIGNATURE [signature]   Date May 15, 2003

TYPED or PRINTED NAME George R. Repper
TELEPHONE : 202-783-6040

REGISTRATION NO. 31,414
Docket Number: 2697-121

USE ONLY FOR FILING PROVISIONAL APPLICATION FOR PATENT

60470420 .052503

2697-121

TREATMENT OR PREVENTION OF RESPIRATORY VIRAL INFECTIONS WITH ALPHA THYMOSIN PEPTIDES

In accordance with one embodiment, the present invention relates to treatment or prevention of respiratory viral infections by administering an alpha thymosin peptide to a patient.

In accordance with another embodiment, the invention relates to treatment or prevention of coronavirus infection by administering an alpha thymosin peptide to a patient.

In accordance with a further embodiment, the invention relates to treatment or prevention of Severe Acute Respiratory Syndrome (SARS) in a patient by administering an alpha thymosin peptide.

Administration for prevention can be to persons at high risk because of contact with suspected disease carriers, or in carriers who are asymptomatic.

Alpha thymosin peptides comprise thymosin alpha 1 (TA1) peptides including naturally occurring TA1 as well as synthetic TA1 and recombinant TA1 having the amino acid sequence of naturally occurring TA1, amino acid sequences substantially similar thereto, or an abbreviated sequence form thereof, and their biologically active analogs having substituted, deleted, elongated, replaced, or otherwise modified sequences which possess bioactivity substantially similar to that of TA1, e.g., a TA1 derived peptide having sufficient amino acid homology with TA1 such that it functions in substantially the same way with substantially the same activity as TA1.

Administration can be by any suitable method, including injection, periodic infusion, continuous infusion, and the

like. Suitable dosages of the alpha thymosin peptide can be in the range of about 0.001-10mg/kg/day.

Because the plasma half-life of subcutaneously injected TA1 is only about two hours, according to one embodiment, a TA1 peptide such as TA1 is administered to a patient in need of immune stimulation so as to substantially continuously maintain an immune stimulating-effective amount of the TA1 peptide in the patient's circulatory system during a substantially longer treatment or prevention period. Although much longer treatment periods are contemplated in accordance with the present invention, embodiments of the invention include substantially continuously maintaining an immune stimulating-effective amount of the TA1 peptide in the patient's circulatory system during treatment periods of at least about 6, 10, 12 hours, or longer. In other embodiments, treatment periods are for at least about a day, and even for a plurality of days, e.g., a week or longer. However, it is contemplated that treatments, as defined above, in which immune stimulating-effective amounts of the TA1 peptide are substantially continuously maintained in the patient's circulatory system, may be separated by non-treatment periods of similar or different durations.

In accordance with one embodiment, the TA1 peptide is continuously infused into a patient, e.g., by intravenous infusion, during the treatment period, so as to substantially continuously maintain an immune stimulating-effective amount of the TA1 peptide in the patient's circulatory system. The infusion may be carried out by any suitable means, such as by minipump.

Alternatively, an injection regimen of the TA1 peptide can be maintained so as to substantially continuously maintain an immune stimulating-effective amount of the TA1 peptide in the patient's circulatory system. Suitable injection regimens may include an injection every 1, 2, 4,

6, etc. hours, so as to substantially continuously maintain the immune stimulating-effective amount of the Thymosin alpha 1 peptide in the patient's circulatory system during the treatment period.

Although it is contemplated that during continuous infusion of the TA1 peptide, administration will be for a substantially longer duration, according to one embodiment the continuous infusion of the TA1 peptide is for a treatment period of at least about 1 hour. More preferably, continuous infusion is carried out for longer periods, such as for periods of at least about 6, 8, 10, 12 hours, or longer. In other embodiments, continuous infusion is for at least about one day, and even for a plurality of days such as for one week or more.

In preferred embodiments, the TA1 peptide is present in a pharmaceutically acceptable liquid carrier, such as water for injection, saline in physiological concentrations, or similar.

The present invention also comprises administration of a physiologically active conjugate comprising a TA1 peptide conjugated to a material which increases half-life of the TA1 peptide in serum of a patient when said conjugate is administered to a patient. The material may be a substantially non-antigenic polymer. Suitable polymers will have a molecular weight within a range of about 200-300,000, preferably within a range of about 1,000-100,000, more preferably within a range of about 5,000-35,000, and most preferably within a range of about 10,000-30,000, with a molecular weight of about 20,000 being particularly preferred.

The polymeric substances included are also preferably water-soluble at room temperature. A non-limiting list of such polymers include polyalkylene oxide homopolymers such as polyethylene glycol (PEG) or polypropylene glycols,

polyoxyethylenated polyols, copolymers thereof and block copolymers thereof, provided that the water solubility of the block copolymers is maintained. Among the substantially non-antigenic polymers, mono-activated, alkyl-terminated polyalkylene oxides (PAO's), such as monomethyl-terminated polyethylene glycols (mPEG's) are contemplated. In addition to mPEG, C_{1-4} alkyl-terminated polymers may also be useful.

As an alternative to PAO-based polymers, effectively non-antigenic materials such as dextran, polyvinyl pyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Those of ordinary skill in the art will realize that the foregoing list is merely illustrative and that all polymer materials having the qualities described herein are contemplated. For purposes of the present invention, "effectively non-antigenic" means all materials understood in the art as being nontoxic and not eliciting an appreciable immunogenic response in mammals.

The polymer may be straight-chain or branched. Polyethylene glycol (PEG) is a particularly preferred polymer.

The polymer can be conjugated to the TA1 peptide by any suitable method. Exemplary methods for conjugating polymers to peptides are disclosed in U.S. Patent Nos. 4,179,337, 4,766,106, 4,917,888, 5,122,614 and 6,177,074, as well as PCT International Publication No. WO 95/13090, all of which are incorporated herein by reference. Thymosin alpha 1 has five separate possible sites for amino group conjugation of a polymer, and polymer(s) can be conjugated at one or a plurality of sites. According to one embodiment, 20,000 molecular weight PEG is conjugated to the N-terminal end of TA1 to form a PEG-TA1. This can be formed by solid phase peptide synthesis of TA1 on insoluble polymeric support beads, as is known in the art, with appropriate side chain

protective groups. After complete synthesis of the TA1 peptide on the beads, the protected TA1 is cleaved from the beads leaving the N-terminus with a free amino group, which is reacted with 20,000 molecular weight PEG. The side chain protective groups then are removed to form a conjugate in accordance with this embodiment of the invention.

The isolation, characterization and use of TA1 peptides is described, for example, in U.S. Patent No. 4,079,127, U.S. Patent No. 4,353,821, U.S. Patent No. 4,148,788 and U.S. Patent No. 4,116,951. Effective amounts of TA1 peptide can be determined by routine dose-titration experiments. TA1 has been found to be safe for humans when administered in doses as high as 16 mg/kg body weight/day. Preferred dosages of TA1 peptide are within the range of 0.001 mg/kg body weight/day to 10 mg/kg body weight/day. According to one embodiment, immune stimulating-effective amounts are at dosages which include the TA1 peptide in an amount within a range of about 0.1-20 mg. Preferred dosages include the TA1 peptide in an amount within the range of about 1-10 mg, more preferably about 1-5mg. The above dosages reflect only the TA1 peptide present in the composition, and not the weight of the polymer conjugated thereto.

Conjugation of a polymer to a TA1 peptide in accordance with the present invention substantially increases the plasma half-life of the peptide.

The TA1 peptide also can be administered with an interferon, such as interferon alpha, wherein interferon alpha-2b is preferred. Suitable dosages of interferon alpha-2b may be in the range of about 1-3MU.

The TA1 peptide also can be administered with other immune stimulators or antiviral agents.

CLAIMS

1. A method of treatment or prevention of a respiratory viral infection in a patient comprising administering to said patient an effective amount of an alpha thymosin peptide.

2. The method of claim 1 wherein said peptide is thymosin alpha 1.

3. A method of treatment or prevention of coronavirus infection in a patient comprising administering to said patient an effective amount of an alpha thymosin peptide.

4. The method of claim 3 wherein said alpha thymosin peptide is thymosin alpha 1.

5. A method of treatment or prevention of Severe Acute Respiratory Syndrome in a patient comprising administering to said patient an effective amount of an alpha thymosin peptide.

6. The method of claim 5 wherein said alpha thymosin peptide is thymosin alpha 1.

ABSTRACT OF THE DISCLOSURE

A Thymosin alpha 1 (TA1) peptide is administered to a patient having, or at risk of a respiratory viral infection, coronavirus infection and/or SARS.

This Page is inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☑ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☑ BLURED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLORED OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REPERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning documents *will not* correct images problems checked, please do not report the problems to the IFW Image Problem Mailbox